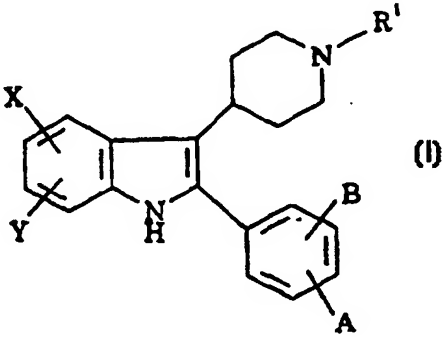




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: C07D 401/04, A61K 31/445	A1	(11) International Publication Number: WO 99/11641 (43) International Publication Date: 11 March 1999 (11.03.99)
(21) International Application Number: PCT/GB98/02552 (22) International Filing Date: 25 August 1998 (25.08.98) (30) Priority Data: 9718712.4 3 September 1997 (03.09.97) GB (71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): MAXEY, Robert, James [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). ROWLEY, Michael [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). VAN NIEL, Monique, Bodil [NL/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). (74) Agents: THOMPSON, John et al.; Merck & Co., Inc., European Patent Dept., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: PHENYLINDOLE DERIVATIVES AS 5-HT _{2A} RECEPTOR ANTAGONISTS (57) Abstract <p>3-(piperidin-4-yl)-1<i>H</i>-indole derivatives of formula (I), or a salt thereof wherein A and B independently represent hydrogen, halogen, cyano, nitro, trifluoromethyl, trifluoromethoxy, C₁₋₆ alkyl, C₁₋₆ alkoxy or amino; or A and B, when attached to adjacent carbon atoms, together represent methylenedioxy; X and Y independently represent hydrogen, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy or phenyl, and R¹ represents C₁₋₆ alkyl or an optionally substituted aryl(C₁₋₆)alkyl group, are selective antagonists of the human 5-HT_{2A} receptor and are therefore useful as pharmaceutical agents, especially in the treatment and/or prevention of adverse conditions of the central nervous system, including psychotic disorders such as schizophrenia.</p> <div style="text-align: center;">  <p>(I)</p> </div>		

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PHENYLINDOLE DERIVATIVES AS 5-HT_{2A} RECEPTOR ANTAGONISTS

The present invention relates to a class of indole derivatives which act on serotonin receptors (also known as 5-hydroxytryptamine or 5-HT
5 receptors). More particularly, the invention concerns 3-(piperidin-4-yl)-1*H*-indole derivatives bearing an optionally substituted phenyl moiety at the 2-position of the indole ring system and an alkyl or aryl-alkyl substituent on the nitrogen atom of the piperidine ring. These compounds are selective antagonists of the human 5-HT_{2A} receptor and are therefore
10 useful as pharmaceutical agents, especially in the treatment and/or prevention of adverse conditions of the central nervous system, including psychotic disorders such as schizophrenia.

Schizophrenia is a disorder which is conventionally treated with drugs known as neuroleptics. In many cases, the symptoms of
15 schizophrenia can be treated successfully with so-called "classical" neuroleptic agents such as haloperidol. Classical neuroleptics generally are antagonists at dopamine D₂ receptors.

Notwithstanding their beneficial antipsychotic effects, classical neuroleptic agents such as haloperidol are frequently responsible for
20 eliciting acute extrapyramidal symptoms (movement disorders) and neuroendocrine (hormonal) disturbances. These side-effects, which plainly detract from the clinical desirability of classical neuroleptics, are believed to be attributable to D₂ receptor blockade in the striatal region of the brain.

25 The compound (+)- α -(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)-ethyl]-4-piperidinemethanol (also known as MDL-100,907) is described in WO 91/18602. In preclinical studies, MDL-100,907 failed to induce catalepsy and failed to block apomorphine-induced stereotyped behaviour in animal models, strongly suggesting that this compound would be free
30 from any liability to cause extrapyramidal side-effects. MDL-100,907 is currently undergoing clinical trials in schizophrenic patients and has

demonstrated efficacy in a multicentre, placebo-controlled study for antipsychotic potential, with no neurological adverse effects.

Pharmacologically, MDL-100,907 has been shown to be a potent antagonist of human 5-HT_{2A} receptors, whilst being essentially devoid of activity at the human dopamine D₂ receptor. It is accordingly believed that compounds which can interact selectively with the 5-HT_{2A} receptor relative to the dopamine D₂ receptor will display the beneficial level of antipsychotic activity associated with 5-HT_{2A} receptor antagonism, whilst minimizing or even avoiding the extrapyramidal and other side-effects arising from an interaction with dopamine D₂ receptors.

The compounds of the present invention are potent antagonists of the human 5-HT_{2A} receptor, and are accordingly of benefit in the treatment and/or prevention of psychotic disorders such as schizophrenia. The compounds of the invention may display more effective binding to the human 5-HT_{2A} receptor than to the human dopamine D₂ receptor, and they can therefore be expected to manifest fewer side-effects than compounds which do not discriminate in their binding affinity as between 5-HT_{2A} and D₂ receptors.

By virtue of their potent human 5-HT_{2A} receptor antagonist activity, the compounds of the present invention are also effective in the treatment of neurological conditions including depression, anxiety, panic disorder, obsessive-compulsive disorder, pain, sleep disorders such as insomnia, eating disorders such as anorexia nervosa, and dependency or acute toxicity associated with narcotic agents such as LSD or MDMA; and cardiovascular conditions including variant angina, Raynaud's phenomenon, intermittent claudication, coronary and peripheral vasospasms, fibromyalgia, cardiac arrhythmias and thrombotic illness. They may also be generally of benefit in the inhibition of platelet aggregation, as well as in controlling the extrapyramidal symptoms associated with the administration of neuroleptic agents. They may further be effective in the lowering of intraocular pressure and may

therefore be beneficial in treating glaucoma (cf. T. Mano *et al.* and H. Takaneka *et al.*, *Investigative Ophthalmology and Visual Science*, 1995, vol. 36, pages 719 and 734 respectively).

5 Being 5-HT_{2A} receptor antagonists, the compounds of the present invention may also be beneficial in preventing or reducing the toxic symptoms associated with the intake of ergovaline in animals consuming *Acremonium coenophialum* infected tall fescue (cf. D. C. Dyer, *Life Sciences*, 1993, 53, 223-228).

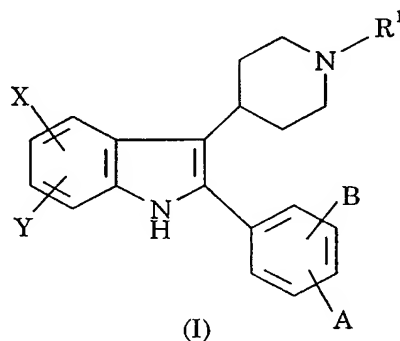
10 In JP-A-3-264581 is described a class of 3-(piperidin-4-yl)-1*H*-indole analogues bearing *inter alia* an optionally substituted phenyl group at the 2-position of the indole nucleus and a heterocyclic moiety attached through an alkylene linkage to the nitrogen atom of the piperidine ring. These compounds are stated therein to have a strong serotonin-2 receptor antagonist action and hence to be useful as medicines for the treatment of
15 diseases of the circulatory system, and of psychiatric diseases such as depression or schizophrenia. There is, however, no disclosure nor any suggestion in JP-A-3-264581 of replacing the precisely defined heterocycl-alkyl substituent on the piperidine ring with an alkyl or aryl-alkyl moiety.

20 GB-1465826 describes a variety of indolylpiperidine-butyrophenones bearing *inter alia* a phenyl group at the 2-position of the indole ring system. These compounds are alleged therein to show activities typical of neuroleptics and therefore to be of potential interest as depressants of the central nervous system, as sedatives and as
25 tranquilizers. However, nowhere in GB-1465826 is there any disclosure or suggestion of replacing the 4-fluorobutyrophenone substituent on the piperidine ring with an alkyl or aryl-alkyl moiety.

The compounds according to the present invention are potent and selective 5-HT_{2A} receptor antagonists having a human 5-HT_{2A} receptor
30 binding affinity (K_i) of 100 nM or less, typically of 50 nM or less and preferably of 10 nM or less. The compounds of the invention may possess

at least a 10-fold selective affinity, suitably at least a 20-fold selective affinity and preferably at least a 50-fold selective affinity, for the human 5-HT_{2A} receptor relative to the human dopamine D₂ receptor.

The present invention provides a compound of formula I, or a salt thereof:



wherein

A and B independently represent hydrogen, halogen, cyano, nitro, trifluoromethyl, trifluoromethoxy, C₁₋₆ alkyl, C₁₋₆ alkoxy or amino; or

A and B, when attached to adjacent carbon atoms, together represent methylenedioxy;

X and Y independently represent hydrogen, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy or phenyl; and

R¹ represents C₁₋₆ alkyl or an optionally substituted aryl(C₁₋₆)alkyl group.

The present invention also provides a compound of formula I as depicted above, or a salt thereof, wherein A and B independently represent hydrogen, halogen, cyano, nitro, trifluoromethyl, trifluoromethoxy, C₁₋₆ alkyl or C₁₋₆ alkoxy; and X, Y and R¹ are as defined above.

Where R¹ represents aryl(C₁₋₆)alkyl, this group may be optionally substituted by one or more substituents. Suitably, the aryl(C₁₋₆)alkyl group R¹ is unsubstituted, or substituted by one, two or three substituents. More particularly, the aryl(C₁₋₆)alkyl group R¹ may be unsubstituted, or substituted by one or two substituents. In general, the aryl(C₁₋₆)alkyl

group R¹ may be unsubstituted or monosubstituted. Any optional substitution on the aryl(C₁₋₆)alkyl group R¹ will suitably be on the aryl moiety thereof, although substitution on the alkyl moiety thereof is an alternative possibility. Examples of optional substituents on the group R¹ include halogen, nitro, trifluoromethyl, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio or di(C₁₋₆)alkylamino.

In an alternative embodiment, the group R¹ may be optionally substituted by one or more substituents selected from halogen, cyano, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₂₋₆ alkoxycarbonyl, C₂₋₆ alkylcarbonyl, C₁₋₆ alkylsulphonyl, arylsulphonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, di(C₁₋₆)alkylaminomethyl, C₂₋₆ alkylcarbonylamino, arylcarbonylamino, C₂₋₆ alkoxycarbonylamino, *N*-(C₁₋₆)alkyl-*N*-(C₂₋₆)alkoxycarbonylamino, C₁₋₆ alkylsulphonylamino, arylsulphonylamino, C₁₋₆ alkylsulphonylaminomethyl, aminocarbonylamino, C₁₋₆ alkylaminocarbonylamino, di(C₁₋₆)alkylaminocarbonylamino, mono- or diarylaminocarbonylamino, pyrrolidinylcarbonylamino, piperidinylcarbonylamino, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl, di(C₁₋₆)alkylaminosulphonyl, aminosulphonylmethyl, C₁₋₆ alkylaminosulphonylmethyl and di(C₁₋₆)alkylaminosulphonylmethyl.

As used herein, the expression "C₁₋₆ alkyl" includes methyl and ethyl groups, and straight-chained or branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, *n*-propyl, isopropyl and *tert*-butyl. Derived expressions such as "C₁₋₆ alkoxy", "C₁₋₆ alkylthio" and "C₁₋₆ alkylamino" are to be construed accordingly.

Typical aryl groups include phenyl and naphthyl, preferably phenyl.

The expression "aryl(C₁₋₆)alkyl" as used herein includes benzyl, phenylethyl, phenylpropyl, naphthylmethyl and naphthylethyl, especially phenylethyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine or chlorine.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in
5 the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable
10 acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include
15 alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the
20 compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

Particular values for the substituent A in the compounds of formula
25 I above include hydrogen, fluoro, trifluoromethyl, methyl and methoxy, especially hydrogen. More particularly, A may represent hydrogen or fluoro, especially hydrogen.

Suitably, B represents hydrogen, fluoro, chloro, cyano, nitro, trifluoromethyl, trifluoromethoxy or amino. In an alternative
30 embodiment, B may represent hydrogen, fluoro, chloro, cyano, nitro,

trifluoromethyl, trifluoromethoxy, methyl or methoxy, especially hydrogen.

In addition, A and B, when attached to adjacent carbon atoms, may together represent methylenedioxy.

- 5 Particular values for the substituent X include hydrogen, fluoro and methoxy, especially hydrogen.

Suitably, Y represents hydrogen, fluoro, chloro, bromo, methyl, methoxy or phenyl, especially hydrogen. More particularly, Y may represent hydrogen, fluoro or chloro, especially hydrogen.

- 10 Suitably, R¹ represents methyl, ethyl, optionally substituted benzyl, optionally substituted phenylethyl or optionally substituted phenylpropyl. In addition, R¹ may represent optionally substituted naphthylethyl.

- Preferably, R¹ represents phenylethyl, which may be unsubstituted, or substituted by one or more substituents. Typically, the phenylethyl
15 group R¹ will be unsubstituted, or substituted by one, two or three (especially one or two) substituents. More preferably, R¹ represents unsubstituted or monosubstituted phenylethyl.

- Examples of specific substituents on the group R¹ include fluoro, chloro, bromo, iodo, nitro, trifluoromethyl, methyl, hydroxy, methoxy,
20 methylthio and dimethylamino.

- Alternatively, typical substituents on the group R¹ include fluoro, chloro, cyano, methoxy, amino, methylamino, dimethylamino, dimethylaminomethyl, acetylamino, methoxycarbonylamino, *tert*-
butoxycarbonylamino, *N*-methoxycarbonyl-*N*-methylamino,
25 methylsulphonylamino, aminocarbonylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulphonyl and methylaminosulphonylmethyl.

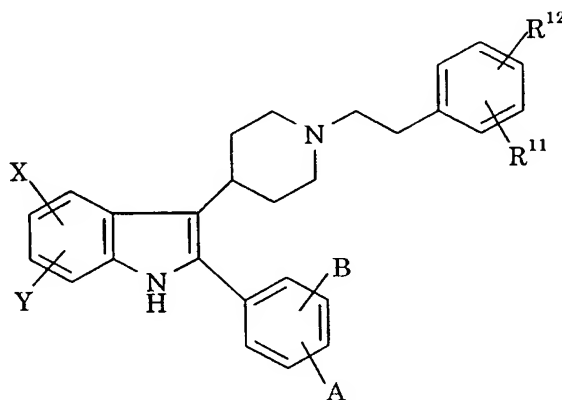
- Representative values of R¹ include methyl, ethyl, benzyl, fluorobenzyl, cyanobenzyl, methoxybenzyl, aminobenzyl,
30 dimethylaminomethyl-benzyl, acetylamino-benzyl, aminocarbonyl-benzyl, methylaminocarbonyl-benzyl, dimethylaminocarbonyl-benzyl,

aminosulphonyl-benzyl, phenylethyl, fluoro-phenylethyl, cyano-phenylethyl, amino-phenylethyl, dimethylamino-phenylethyl, acetyl-amino-phenylethyl, methoxycarbonylamino-phenylethyl, (*N*-methoxycarbonyl-*N*-methyl)amino-phenylethyl, aminocarbonylamino-phenylethyl and phenylpropyl (especially 2-phenylpropyl).

Particular values of R^1 include methyl, benzyl and phenylethyl. A more particular value of R^1 is 2-phenylethyl.

Specific values of R^1 include phenylethyl, fluoro-phenylethyl, chloro-phenylethyl, bromo-phenylethyl, iodo-phenylethyl, difluoro-phenylethyl, dichloro-phenylethyl, (chloro)(fluoro)-phenylethyl, (fluoro)-(trifluoromethyl)-phenylethyl, (bromo)(methoxy)-phenylethyl, trifluoro-phenylethyl, nitro-phenylethyl, methyl-phenylethyl, hydroxy-phenylethyl, methoxy-phenylethyl, dimethoxy-phenylethyl, (hydroxy)(methoxy)-phenylethyl, (hydroxy)(dimethoxy)-phenylethyl, trimethoxy-phenylethyl, methylthio-phenylethyl, dimethylamino-phenylethyl, phenylpropyl, hydroxy-phenylpropyl and naphthylethyl.

A particular sub-class of compounds according to the invention is represented by the compounds of formula II, and salts thereof:



(II)

wherein

A, B, X and Y are as defined with reference to formula I above; and

R¹¹ and R¹² independently represent hydrogen, halogen, nitro, trifluoromethyl, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio or di(C₁₋₆)alkylamino.

5 The present invention also provides a compound of formula II as depicted above, or a salt thereof, wherein R¹¹ and R¹² independently represent hydrogen, halogen, C₁₋₆ alkyl or C₁₋₆ alkoxy; and A, B, X and Y are as defined above.

Suitably, R¹¹ represents hydrogen, fluoro, chloro or methoxy, especially hydrogen. More particularly, R¹¹ may represent hydrogen or
10 fluoro, especially hydrogen.

Suitably, R¹² represents hydrogen, fluoro, chloro, bromo, iodo, nitro, trifluoromethyl, methyl, hydroxy, methoxy, methylthio or dimethylamino. More particularly, R¹² may represent hydrogen, fluoro, chloro, methyl or methoxy, especially hydrogen.

15 Specific compounds within the scope of the present invention include:

- 3-(1-methylpiperidin-4-yl)-2-phenyl-1*H*-indole;
- 3-(1-benzylpiperidin-4-yl)-2-phenyl-1*H*-indole;
- 2-phenyl-3-[1-(2-phenylethyl)piperidin-4-yl]-1*H*-indole;
- 20 5-chloro-3-[1-(2-phenylethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(3-fluorophenyl)-1*H*-indole;
- 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(2-fluorophenyl)-1*H*-indole;
- 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(2,3-difluorophenyl)-1*H*-indole;
- 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(3,4-difluorophenyl)-1*H*-indole;
- 25 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(2,4-difluorophenyl)-1*H*-indole;
- 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(4-fluorophenyl)-1*H*-indole;
- 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(3,5-difluorophenyl)-1*H*-indole;
- 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(2,5-difluorophenyl)-1*H*-indole;
- 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(3-chlorophenyl)-1*H*-indole;
- 30 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(3-nitrophenyl)-1*H*-indole;
- 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(3-trifluoromethylphenyl)-1*H*-indole;

- 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(3,4-methylenedioxyphenyl)-1*H*-indole;
- 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(3-cyanophenyl)-1*H*-indole;
- 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(3-trifluoromethoxyphenyl)-1*H*-indole;
- 5 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(3-aminophenyl)-1*H*-indole;
- 3-[1-(2-(2-fluorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-(3-fluorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-(4-fluorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(1-hydroxy-3-phenylprop-2-yl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 10 6-chloro-3-[1-(2-phenylethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 6-fluoro-3-[1-(2-phenylethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 4-fluoro-3-[1-(2-phenylethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 7-fluoro-3-[1-(2-phenylethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-(2,3,5-trifluorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 15 3-[1-(2-(2-hydroxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-(3-hydroxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-(3-nitrophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-(4-dimethylaminophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-(4-methylthiophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 20 3-[1-(2-(3-methoxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-(naphth-1-yl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-(4-bromophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-(3,4-dichlorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-(2-chloro-4-fluorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 25 3-[1-(2-(3,4-dimethoxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-(3,4,5-trimethoxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-(3-methylphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-(2,4-dichlorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-(2,4-difluorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 30 3-[1-(2-(5-bromo-2-methoxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;

- 3-[1-(2-(2-fluoro-4-trifluoromethylphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-(3-chlorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-(4-iodophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 5 3-[1-(2-(3-bromophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-(4-nitrophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-(4-hydroxy-3,5-dimethoxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-(4-hydroxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 10 3-[1-(2-(4-hydroxy-3-methoxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(3-hydroxy-3-phenylpropyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-(3,4-difluorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-(2-chlorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 15 3-[1-(2-(2-bromophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-fluoro-2-phenylethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(2-(4-chlorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 3-[1-(3-phenylpropyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- 6-fluoro-3-[1-(2-phenylethyl)piperidin-4-yl]-2-(2-fluorophenyl)-1*H*-indole;
- 20 5-fluoro-3-[1-(2-phenylethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
- and salts thereof.

The invention also provides pharmaceutical compositions comprising one or more of the compounds according to this invention in association with a pharmaceutically acceptable carrier. Preferably these

25 compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation.

30 Alternatively, the compositions may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble

salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. An erodible polymer containing the active ingredient may be envisaged. For preparing solid compositions such as tablets, the principal active ingredient is mixed
5 with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a
10 pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation
15 composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Favoured unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise
20 compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner
25 component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present
30 invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil

suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as

5 tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of schizophrenia, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be

10 administered on a regimen of 1 to 4 times per day.

If desired, the compounds according to this invention may be co-administered with another anti-schizophrenic medicament, for example one producing its effects *via* dopamine D₂ and/or D₄ receptor subtype blockade. In such circumstances, an enhanced anti-schizophrenic effect

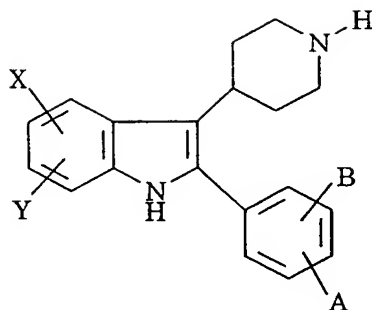
15 may be envisaged without a corresponding increase in side-effects such as those caused by, for example, D₂ receptor subtype blockade; or a comparable anti-schizophrenic effect with reduced side-effects may alternatively be envisaged. Such co-administration may be desirable where a patient is already established on an anti-schizophrenic treatment

20 regime involving conventional anti-schizophrenic medicaments. Suitable anti-schizophrenic medicaments of use in combination with the compounds according to the present invention include haloperidol, chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, chlorprothixene, thiothixene, clozapine, olanzapine,

25 pimozone, molindone, loxapine, sulpiride, risperidone, xanomeline, fananserin and ziprasidone, and pharmaceutically acceptable salts thereof.

The compounds according to the present invention may be prepared by a process which comprises attachment of the R¹ moiety to a compound of formula III:

30



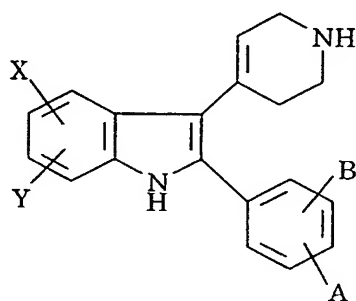
(III)

wherein A, B, X and Y are as defined above; by conventional means including N-alkylation.

- 5 Attachment of the R^1 moiety to the compounds of formula III may conveniently be effected by standard alkylation techniques. One example thereof comprises treatment with an alkyl halide such as methyl iodide, or an aryl(C_{1-6})alkyl halide such as benzyl bromide or 2-phenylethyl bromide, typically under basic conditions, e.g. potassium carbonate or caesium
- 10 carbonate in *N,N*-dimethylformamide. Another example comprises treatment of the compound of formula III with an aryl(C_{1-6})alkyl mesylate such as 2-phenylethyl methanesulphonate, typically in the presence of sodium carbonate and sodium iodide, in a suitable solvent such as 1,2-dimethoxyethane.
- 15 Alternatively, the R^1 moiety may conveniently be attached by reductive alkylation, which may be accomplished in a single step, or as a two-step procedure. The single-step approach suitably comprises treating the required compound of formula III as defined above with the appropriate aldehyde, e.g. formaldehyde, benzaldehyde or
- 20 phenylacetaldehyde, in the presence of a reducing agent such as sodium cyanoborohydride. In a typical two-step procedure, for the preparation of a compound of formula I wherein R^1 corresponds to a group of formula $-CH_2R^{1a}$, a carboxylic acid derivative of formula $R^{1a}-CO_2H$ is condensed with the required compound of formula III, suitably in the presence of
- 25 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and

1-hydroxybenzotriazole hydrate, to afford a compound corresponding to formula I wherein R^1 represents $-\text{COR}^{1a}$; the carbonyl group thereof can then be reduced, for example by treatment with diisobutylaluminium hydride, and the required compound of formula I thereby obtained.

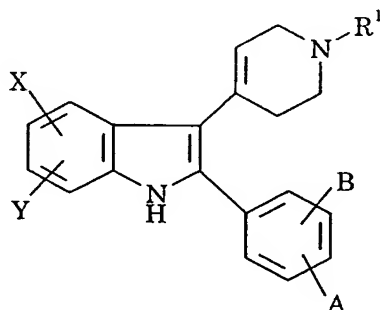
- 5 The compounds of formula III above may be prepared by reduction of the corresponding compound of formula IV:



(IV)

- 10 wherein A, B, X and Y are as defined above.

Similarly, the compounds according to the invention may be prepared by a process which comprises reducing a compound of formula V:



(V)

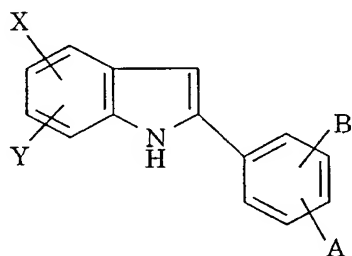
15

wherein A, B, X, Y and R^1 are as defined above.

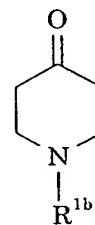
Reduction of the compounds of formula IV or V may conveniently be accomplished by conventional catalytic hydrogenation, which comprises treating the appropriate compound with hydrogen in the presence of a

hydrogenation catalyst such as palladium on charcoal. Alternatively, compound IV or V may be reduced by transfer hydrogenation using a hydrogenation catalyst such as palladium on charcoal in the presence of a hydrogen donor such as ammonium formate, typically in a lower alkanol solvent such as methanol.

The intermediates of formula IV and V may be prepared by reacting a compound of formula VI with the appropriate piperidinone derivative of formula VII:



(VI)



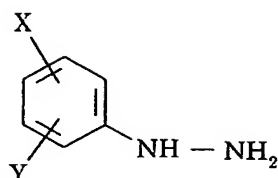
(VII)

wherein A, B, X and Y are as defined above, and R^{1b} represents hydrogen or corresponds to the moiety R¹ as defined above.

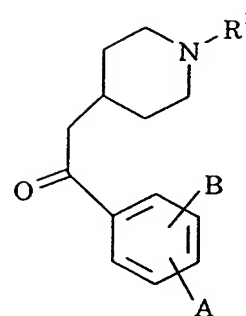
The reaction between compounds VI and VII is conveniently effected by heating the reactants under acidic conditions, typically in a mixture of phosphoric acid and acetic acid at a temperature in the region of 80°C.

The intermediates of formula III and of formula V above are novel compounds in their own right, and represent further features of the present invention.

In another procedure, the compounds according to the invention may be prepared by a process which comprises reacting a compound of formula VIII or an acid addition salt thereof, typically the hydrochloride salt, with a compound of formula IX:



(VIII)

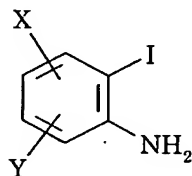


(IX)

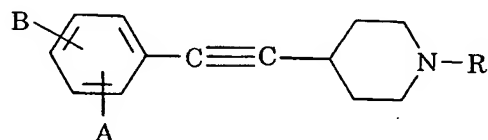
wherein A, B, X, Y and R¹ are as defined above.

The reaction between compounds VIII and IX, which is an example
 5 of the well-known Fischer indole synthesis, is suitably effected by stirring
 in ethanol at 25°C, followed by heating in trifluoroacetic acid at 70°C.

In a further procedure, the compounds according to the invention
 may be prepared by a process which comprises reacting a compound of
 formula X with a compound of formula XI (cf. Larock and Yum, *J. Am.*
 10 *Chem. Soc.*, 1991, 113, 6689):



(X)



(XI)

wherein A, B, X, Y and R¹ are as defined above; in the presence of a
 15 transition metal catalyst.

The transition metal catalyst employed in the reaction between
 compounds X and XI is suitably a palladium-containing catalyst. Typical
 catalysts include palladium(II) acetate, optionally in the presence of
 triphenylphosphine, and dichlorobis(triphenylphosphine)palladium(II). A
 20 preferred catalyst is dichlorobis(triphenylphosphine)palladium(II).

The transition metal catalysed indole formation reaction between compounds X and XI is advantageously carried out under basic conditions. Typical basic reagents of use in the reaction include sodium carbonate, potassium carbonate, sodium acetate or potassium acetate, optionally in the presence of lithium chloride or tetra-*n*-butylammonium chloride; and tetramethylguanidine. A preferred base is tetramethylguanidine. The reaction is conveniently effected in a polar aprotic organic solvent such as *N,N*-dimethylformamide, typically at an elevated temperature, e.g. a temperature in the region of 80-110°C.

Where they are not commercially available, the starting materials of formula VI, VII, VIII, IX, X and XI may be prepared by procedures analogous to those described in the accompanying Examples, or by standard methods well known from the art.

It will be appreciated that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further desired compound of formula I using techniques known from the art.

Where the above-described processes for the preparation of the compounds of use in the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-*p*-toluoyl-*d*-tartaric acid and/or (+)-di-*p*-toluoyl-*l*-tartaric acid, followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic*
5 *Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

10 The following Examples illustrate the preparation of compounds of use in the invention.

The compounds in accordance with this invention potentially inhibit [3H]-ketanserin binding to the human 5-HT_{2A} receptor expressed in clonal cell lines. Moreover, those compounds of the invention which have been tested display a selective affinity for the 5-HT_{2A} receptor relative to the
15 dopamine D₂ receptor.

The compounds of the accompanying Examples were all found to possess a K_i value for displacement of [3H]-ketanserin from the human 5-HT_{2A} receptor, when expressed in Chinese hamster ovary (CHO) clonal cell lines, of 100 nM or less.

20

EXAMPLE 1

3-(1-Methylpiperidin-4-yl)-2-phenyl-1H-indole

25 Step 1: 3-(1,2,3,6-Tetrahydropyridin-4-yl)-2-phenyl-1H-indole

2-Phenylindole (25 g, 130 mmol) was stirred at 80°C in AcOH (200 ml), and 4-piperidone hydrochloride hydrate (50 g, 376 mmol) and 1M phosphoric acid (100 ml) added. After a further 6 h, the mixture was poured into ice/ammonia, and extracted with EtOAc (3 x 200 ml). The
30 combined organic layers were washed with water and brine, dried, and evaporated *in vacuo* to give a pale yellow solid. This was suspended in

boiling EtOAc (200 ml), cooled to room temperature overnight, and the solid collected, washed with EtOAc and dried to give the *title compound* (26 g, 73%) as a pale yellow solid; δ_H (360MHz, d_6 -DMSO) 2.00-2.10 (2H, m, NCH_2CH_2), 2.89 (2H, t, J 5, NCH_2CH_2), 3.40-3.45 (2H, m, NCH_2CH),
5 5.78 (1H, br s, NCH_2CH), 7.00 (1H, t, J 7, indole-H), 7.08 (1H, t, J 7, indole-H), 7.20-7.50 (5H, m, ArH), 7.69 (2H, d, J 7, ArH), 11.3 (1H, br s, indole NH); m/z (ES⁺) 275 ($M^+ + H$).

Step 2: 3-(Piperidin-4-yl)-2-phenyl-1H-indole

10 3-(1,2,3,6-Tetrahydropyridin-4-yl)-2-phenyl-1H-indole (25 g, 91 mmol), palladium on carbon (10% w/w, 2.5 g) and NH_4HCO_2 (57 g, 0.72 mol) were refluxed in MeOH (300 ml) for 8 h. Palladium on carbon (10% w/w, 1.25 g) and NH_4HCO_2 (29 g, 0.36 mol) were added, and refluxing continued for 8 h. The mixture was cooled, filtered, and evaporated to give
15 a white solid. This was suspended in H_2O (1 l) and 1M NaOH (100 ml), and the mixture extracted with CH_2Cl_2 (5 x 150 ml). The combined organic layers were washed with water and brine, dried, and evaporated *in vacuo* to give a white solid, which was recrystallised from MeOH (300 ml) and H_2O (100 ml) to give the *title compound* (19 g, 75%) as white
20 crystals, mp 187-188°C. Oxalate salt, white crystals, mp 209-211°C (from EtOH). Found C, 69.09; H, 6.65; N, 7.52. $C_{19}H_{20}N_2 \cdot C_2H_2O_4$ requires C, 68.84; H, 6.05; N, 7.65%; δ_H (360MHz, d_6 -DMSO) 1.80 (2H, d, J 13, NCH_2CH_{AHB}), 2.30-2.50 (2H, m, NCH_2CH_{AHB}), 2.91 (2H, t, J 12, NCH_{AHB}), 3.10-3.20 (1H, m, CH_2CH), 3.32 (2H, d, J 12, NCH_{AHB}), 6.98
25 (1H, t, J 7, indole-H), 7.08 (1H, t, J 7, indole-H), 7.20-7.50 (6H, m, ArH), 7.88 (1H, d, J 7, ArH), 11.3 (1H, br s, indole NH); m/z (ES⁺) 277 ($M^+ + H$).

Step 3: 3-(1-Methylpiperidin-4-yl)-2-phenyl-1H-indole

30 3-(Piperidin-4-yl)-2-phenyl-1H-indole (200 mg, 0.7 mmol), sodium cyanoborohydride (51 mg, 0.8 mmol), formaldehyde (60 μ l, 40% in H_2O , 0.8 mmol) and AcOH (97 μ l, 1.7 mmol) were stirred in MeOH (5 ml) at 0°C for

1 h, then room temperature for 2 h. The solution was poured into saturated NaHCO₃ solution and extracted with EtOAc. The organic layer was washed with water and brine, dried, and evaporated *in vacuo* to give white crystals (49 mg, 23%), mp 245-246°C (from EtOH); δ_H (360MHz, d₆-DMSO) 1.88 (2H, d, *J* 13, NCH₂CH_AH_B), 2.60-2.80 (2H, m, NCH₂CH_AH_B), 2.76 (3H, s, CH₃), 3.00-3.20 (3H, m, CH₂CH and NCH_AH_B), 3.44 (2H, d, *J* 12, NCH_AH_B), 6.99 (1H, t, *J* 7, indole-H), 7.09 (1H, t, *J* 7, indole-H), 7.20-7.50 (6H, m, ArH), 7.98 (1H, d, *J* 7, ArH), 11.20 (1H, br s, indole NH); *m/z* (ES⁺) 291 (*M*⁺+H).

10

EXAMPLE 2

3-(1-Benzylpiperidin-4-yl)-2-phenyl-1H-indole

3-(Piperidin-4-yl)-2-phenyl-1H-indole (150 mg, 0.54 mmol), benzyl bromide (80 μ l, 0.66 mmol), and K₂CO₃ (0.15 g, 1.08 mmol) were stirred in DMF (3 ml) at room temperature overnight. The mixture was poured into water and extracted with EtOAc. The organic layer was washed with water and brine, dried, evaporated *in vacuo* and purified by flash chromatography eluting with CH₂Cl₂:MeOH (93:7 v/v) to give the product as a solid (129 mg, 65%): oxalate salt, white crystals, mp 160-164°C (dec.) (from MeOH). Found C, 70.87; H, 6.13; N, 5.93. C₂₆H₂₆N₂.C₂H₂O₄.H₂O requires C, 70.87; H, 6.37; N, 5.90%; δ_H (360MHz, d₆-DMSO) 2.00 (2H, d, *J* 13, NCH₂CH_AH_B), 2.60-2.80 (2H, m, NCH₂CH_AH_B), 3.00-3.10 (2H, m, NCH_AH_B), 3.20-3.30 (1H, m, CH₂CH), 3.50-3.60 (2H, m, NCH_AH_B), 4.39 (2H, s, PhCH₂), 7.12 (1H, t, *J* 7, indole-H), 7.23 (1H, t, *J* 7, indole-H), 7.50-7.70 (11H, m, ArH), 8.00 (1H, d, *J* 8, ArH), 11.20 (1H, br s, indole NH); *m/z* (ES⁺) 367 (*M*⁺+H).

25

EXAMPLE 3

2-Phenyl-3-[1-(2-phenylethyl)piperidin-4-yl]-1H-indole

3-(Piperidin-4-yl)-2-phenyl-1H-indole (150 mg, 0.54 mmol),
5 phenethyl bromide (90 μ l, 0.64 mmol), and K_2CO_3 (0.15 g, 1.08 mmol) were
stirred in DMF (3 ml) at room temperature overnight. The mixture was
poured into water and extracted with EtOAc. The organic layer was
washed with water and brine, dried, evaporated *in vacuo* and purified by
flash chromatography eluting with CH_2Cl_2 :MeOH (93:7 v/v) to give the
10 product (189 mg, 91 %): oxalate salt, white crystals, mp 209-211°C (dec.)
(from MeOH/Et₂O). Found C, 71.43; H, 6.44; N, 6.02. $C_{27}H_{28}N_2 \cdot C_2H_2O_4$.
 H_2O requires C, 71.29; H, 6.60; N, 5.73%; δ_H (360MHz, d_6 -DMSO) 1.92
(2H, d, J 13, $NCH_2CH_AH_B$), 2.50-2.70 (2H, m, $NCH_2CH_AH_B$), 2.90-3.10
(4H, m, CH_2), 3.10-3.20 (1H, m, CH_2CH), 3.20-3.30 (2H, m, CH_2), 3.60 (2H,
15 d, J 12, NCH_AH_B), 7.00 (1H, t, J 7, indole-H), 7.10 (1H, t, J 7, indole-H),
7.50-7.70 (11H, m, ArH), 7.88 (1H, d, J 8, ArH), 11.20 (1H, br s, indole
NH); m/z (ES⁺) 381 (M^++H).

EXAMPLES 4 TO 61

20

The following compounds were prepared by methods analogous to
those described above.

Example 4: 5-Chloro-3-[1-(2-phenylethyl)piperidin-4-yl]-2-phenyl-1H-
25 indole

Example 5: 3-[1-(2-Phenylethyl)piperidin-4-yl]-2-(3-fluorophenyl)-1H-
indole

Example 6: 3-[1-(2-Phenylethyl)piperidin-4-yl]-2-(2-fluorophenyl)-1H-
indole

30 *Example 7:* 3-[1-(2-Phenylethyl)piperidin-4-yl]-2-(2,3-difluorophenyl)-1H-
indole

Example 8: 3-[1-(2-Phenylethyl)piperidin-4-yl]-2-(3,4-difluorophenyl)-1*H*-indole

Example 9: 3-[1-(2-Phenylethyl)piperidin-4-yl]-2-(2,4-difluorophenyl)-1*H*-indole

5 *Example 10:* 3-[1-(2-Phenylethyl)piperidin-4-yl]-2-(4-fluorophenyl)-1*H*-indole

Example 11: 3-[1-(2-Phenylethyl)piperidin-4-yl]-2-(3,5-difluorophenyl)-1*H*-indole

10 *Example 12:* 3-[1-(2-Phenylethyl)piperidin-4-yl]-2-(2,5-difluorophenyl)-1*H*-indole

Example 13: 3-[1-(2-Phenylethyl)piperidin-4-yl]-2-(3-chlorophenyl)-1*H*-indole

Example 14: 3-[1-(2-Phenylethyl)piperidin-4-yl]-2-(3-nitrophenyl)-1*H*-indole

15 *Example 15:* 3-[1-(2-Phenylethyl)piperidin-4-yl]-2-(3-trifluoromethylphenyl)-1*H*-indole

Example 16: 3-[1-(2-Phenylethyl)piperidin-4-yl]-2-(3,4-methylenedioxyphenyl)-1*H*-indole

20 *Example 17:* 3-[1-(2-Phenylethyl)piperidin-4-yl]-2-(3-cyanophenyl)-1*H*-indole

Example 18: 3-[1-(2-Phenylethyl)piperidin-4-yl]-2-(3-trifluoromethoxyphenyl)-1*H*-indole

Example 19: 3-[1-(2-Phenylethyl)piperidin-4-yl]-2-(3-aminophenyl)-1*H*-indole

25 *Example 20:* 3-[1-(2-(2-Fluorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 21: 3-[1-(2-(3-Fluorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

30 *Example 22:* 3-[1-(2-(4-Fluorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 23: 3-[1-(1-Hydroxy-3-phenylprop-2-yl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 24: 6-Chloro-3-[1-(2-phenylethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

5 *Example 25:* 6-Fluoro-3-[1-(2-phenylethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 26: 4-Fluoro-3-[1-(2-phenylethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

10 *Example 27:* 7-Fluoro-3-[1-(2-phenylethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 28: 3-[1-(2-(2,3,5-Trifluorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 29: 3-[1-(2-(2-Hydroxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

15 *Example 30:* 3-[1-(2-(3-Hydroxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 31: 3-[1-(2-(3-Nitrophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

20 *Example 32:* 3-[1-(2-(4-Dimethylaminophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 33: 3-[1-(2-(4-Methylthiophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 34: 3-[1-(2-(3-Methoxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

25 *Example 35:* 3-[1-(2-(Naphth-1-yl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 36: 3-[1-(2-(4-Bromophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 37: 3-[1-(2-(3,4-Dichlorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

30 *Example 38:* 3-[1-(2-(2-Chloro-4-fluorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 39: 3-[1-(2-(3,4-Dimethoxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 40: 3-[1-(2-(3,4,5-Trimethoxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

5 *Example 41:* 3-[1-(2-(3-Methylphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 42: 3-[1-(2-(2,4-Dichlorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

10 *Example 43:* 3-[1-(2-(2,4-Difluorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 44: 3-[1-(2-(5-Bromo-2-methoxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 45: 3-[1-(2-(2-Fluoro-4-trifluoromethylphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

15 *Example 46:* 3-[1-(2-(3-Chlorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 47: 3-[1-(2-(4-Iodophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 48: 3-[1-(2-(3-Bromophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

20 *Example 49:* 3-[1-(2-(4-Nitrophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 50: 3-[1-(2-(4-Hydroxy-3,5-dimethoxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

25 *Example 51:* 3-[1-(2-(4-Hydroxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 52: 3-[1-(2-(4-Hydroxy-3-methoxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 53: 3-[1-(3-Hydroxy-3-phenylpropyl)piperidin-4-yl]-2-phenyl-1*H*-indole

30 *Example 54:* 3-[1-(2-(3,4-Difluorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 55: 3-[1-(2-(2-Chlorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 56: 3-[1-(2-(2-Bromophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

5 *Example 57:* 3-[1-(2-Fluoro-2-phenylethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

Example 58: 3-[1-(2-(4-Chlorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

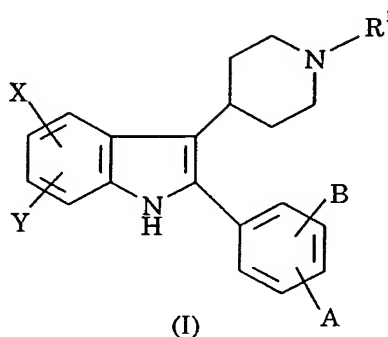
Example 59: 3-[1-(3-Phenylpropyl)piperidin-4-yl]-2-phenyl-1*H*-indole

10 *Example 60:* 6-Fluoro-3-[1-(2-phenylethyl)piperidin-4-yl]-2-(2-fluorophenyl)-1*H*-indole

Example 61: 5-Fluoro-3-[1-(2-phenylethyl)piperidin-4-yl]-2-phenyl-1*H*-indole

CLAIMS:

1. A compound of formula I, or a salt thereof:



5

wherein

A and B independently represent hydrogen, halogen, cyano, nitro, trifluoromethyl, trifluoromethoxy, C₁₋₆ alkyl, C₁₋₆ alkoxy or amino; or

- 10 A and B, when attached to adjacent carbon atoms, together represent methylenedioxy;

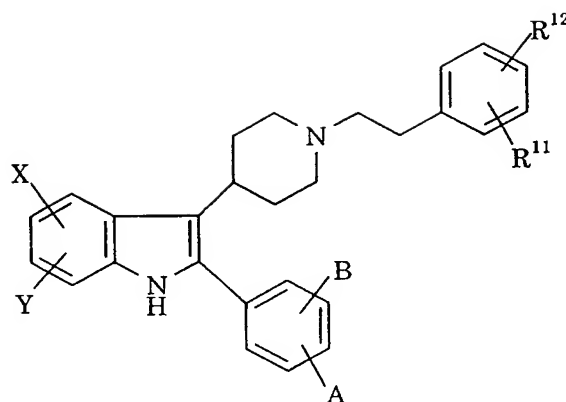
X and Y independently represent hydrogen, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy or phenyl; and

- 15 R¹ represents C₁₋₆ alkyl or an optionally substituted aryl(C₁₋₆)alkyl group.

2. A compound as claimed in claim 1 wherein R¹ represents phenylethyl, either unsubstituted or substituted by one, two or three substituents selected from halogen, nitro, trifluoromethyl, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio or di(C₁₋₆)alkylamino.
- 20

3. A compound as claimed in claim 2 wherein R¹ represents 2-phenylethyl.

- 25 4. A compound as claimed in claim 1 represented by formula II, and salts and prodrugs thereof:



(II)

wherein

- 5 A, B, X and Y are as defined in claim 1; and
 R¹¹ and R¹² independently represent hydrogen, halogen, nitro, trifluoromethyl, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio or di(C₁₋₆)alkylamino.

- 10 5. A compound selected from:
 3-(1-methylpiperidin-4-yl)-2-phenyl-1*H*-indole;
 3-(1-benzylpiperidin-4-yl)-2-phenyl-1*H*-indole;
 2-phenyl-3-[1-(2-phenylethyl)piperidin-4-yl]-1*H*-indole;
 and salts thereof.

- 15 6. A compound selected from:
 5-chloro-3-[1-(2-phenylethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(3-fluorophenyl)-1*H*-indole;
 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(2-fluorophenyl)-1*H*-indole;
 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(2,3-difluorophenyl)-1*H*-indole;
 20 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(3,4-difluorophenyl)-1*H*-indole;
 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(2,4-difluorophenyl)-1*H*-indole;
 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(4-fluorophenyl)-1*H*-indole;

- 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(3,5-difluorophenyl)-1*H*-indole;
3-[1-(2-phenylethyl)piperidin-4-yl]-2-(2,5-difluorophenyl)-1*H*-indole;
3-[1-(2-phenylethyl)piperidin-4-yl]-2-(3-chlorophenyl)-1*H*-indole;
3-[1-(2-phenylethyl)piperidin-4-yl]-2-(3-nitrophenyl)-1*H*-indole;
5 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(3-trifluoromethylphenyl)-1*H*-indole;
3-[1-(2-phenylethyl)piperidin-4-yl]-2-(3,4-methylenedioxyphenyl)-1*H*-indole;
3-[1-(2-phenylethyl)piperidin-4-yl]-2-(3-cyanophenyl)-1*H*-indole;
3-[1-(2-phenylethyl)piperidin-4-yl]-2-(3-trifluoromethoxyphenyl)-1*H*-indole;
10 3-[1-(2-phenylethyl)piperidin-4-yl]-2-(3-aminophenyl)-1*H*-indole;
3-[1-(2-(2-fluorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-(3-fluorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-(4-fluorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(1-hydroxy-3-phenylprop-2-yl)piperidin-4-yl]-2-phenyl-1*H*-indole;
15 6-chloro-3-[1-(2-phenylethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
6-fluoro-3-[1-(2-phenylethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
4-fluoro-3-[1-(2-phenylethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
7-fluoro-3-[1-(2-phenylethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-(2,3,5-trifluorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
20 3-[1-(2-(2-hydroxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-(3-hydroxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-(3-nitrophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-(4-dimethylaminophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-(4-methylthiophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
25 3-[1-(2-(3-methoxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-(naphth-1-yl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-(4-bromophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-(3,4-dichlorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-(2-chloro-4-fluorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
30 3-[1-(2-(3,4-dimethoxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;

- 3-[1-(2-(3,4,5-trimethoxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-(3-methylphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-(2,4-dichlorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-(2,4-difluorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
5 3-[1-(2-(5-bromo-2-methoxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-(2-fluoro-4-trifluoromethylphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-(3-chlorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
10 3-[1-(2-(4-iodophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-(3-bromophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-(4-nitrophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-(4-hydroxy-3,5-dimethoxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
15 3-[1-(2-(4-hydroxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-(4-hydroxy-3-methoxyphenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(3-hydroxy-3-phenylpropyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-(3,4-difluorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
20 3-[1-(2-(2-chlorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-(2-bromophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-fluoro-2-phenylethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(2-(4-chlorophenyl)ethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
3-[1-(3-phenylpropyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
25 6-fluoro-3-[1-(2-phenylethyl)piperidin-4-yl]-2-(2-fluorophenyl)-1*H*-indole;
5-fluoro-3-[1-(2-phenylethyl)piperidin-4-yl]-2-phenyl-1*H*-indole;
and salts thereof.

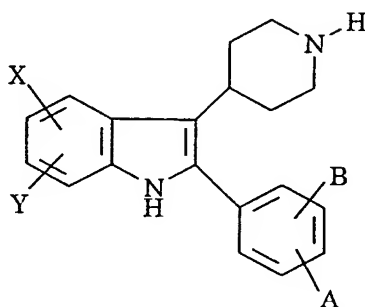
7. A pharmaceutical composition comprising a compound of
30 formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable carrier.

8. A composition as claimed in claim 7 further comprising another anti-schizophrenic medicament.

5 9. The use of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment and/or prevention of psychotic disorders.

10 10. A process for the preparation of a compound as claimed in claim 1 which comprises:

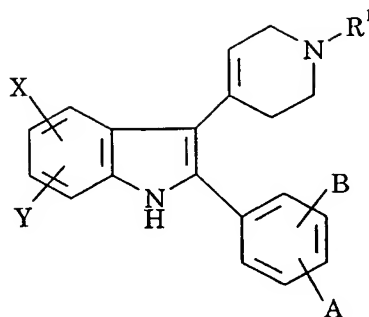
(A) attachment of the R¹ moiety to a compound of formula III:



(III)

15 wherein A, B, X and Y are as defined in claim 1; or

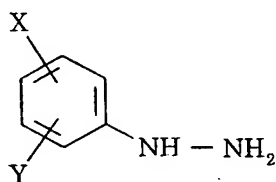
(B) reducing a compound of formula V:



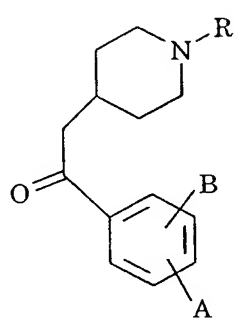
(V)

wherein A, B, X, Y and R¹ are as defined in claim 1; or

- 5 (C) reacting a compound of formula VIII or an acid addition salt thereof with a compound of formula IX:



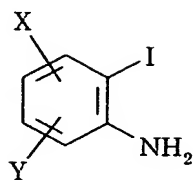
(VIII)



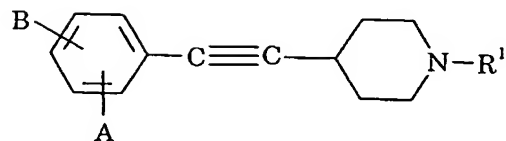
(IX)

- 10 wherein A, B, X, Y and R¹ are as defined in claim 1; or

(D) reacting a compound of formula X with a compound of formula XI:



(X)



(XI)

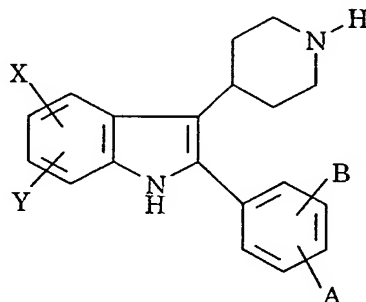
wherein A, B, X, Y and R¹ are as defined in claim 1; in the presence of a transition metal catalyst; and

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(E) subsequently, where required, converting a compound of formula I initially obtained into a further compound of formula I by conventional methods.

10

11. A compound of formula III:

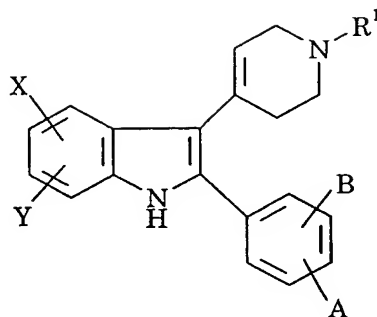


(III)

wherein A, B, X and Y are as defined in claim 1.

15

12. A compound of formula V:



(V)

wherein A, B, X, Y and R¹ are as defined in claim 1.

- 5 13 . A method for the treatment and/or prevention of psychotic disorders which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PO B 98/02552

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/04 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 747 379 A (ADIR ET COMPAGNIE) 11 December 1996 see page 13; claim 1 ----	1,7,9
A	WO 91 18602 A (MERRELL DOW PHARMACEUTICALS INC.) 12 December 1991 cited in the application see page 2 -----	1,7,9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

27 October 1998

Date of mailing of the international search report

09/11/1998

Name and mailing address of the ISA

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Authorized officer

Van Bijlen, H

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 98/ 02552

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 13
is directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PC 98/02552

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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